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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,328	11/12/2003	Alison Hannah	072121-0366	6441

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
08/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,328	HANNAH ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,49-51,53-58 and 67-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,49-51,53-58 and 67-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 6/5/2008, are acknowledged and entered. Claims 59-62 and 64-66 have been cancelled by Applicant. Claims 67-71 are newly presented. Claims 1-38, 49-51, 53-58, and 67-71 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 59-62 and 64-66 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 53-55 and 64 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of Applicant's amendments.

The rejection of claims 1-38, 49-51, 53-62, and 64-66 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cancers wherein the cancer cells express receptor tyrosine kinases selected from FLT-1, VEGFR2, VEGF3, FGFR3, FGFR1, c-kit, and/or FLT-3, does not reasonably provide enablement for treating cancers wherein the cancer cells express other receptor tyrosine kinases, is **withdrawn** in view of Applicant's amendments.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9-13, 16-38, 49-51, 53-58, and 67-71 are rejected under 35 U.S.C. 103(a) as being obvious over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) in view of **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"** (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18).

The applied reference (Renhowe *et al.*) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome

by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims recite methods of treating cancers comprising cells expressing a receptor tyrosine kinase selected from the group consisting of FLT-1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, and FLT-3, comprising administering 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one in amounts to provide ranges of C_{max}, ng/mL, and AUC values as recited in the instant claims. Upon further consideration of the claimed invention, the Examiner is not convinced that the claimed C_{max}, ng/mL, and AUC ranges are a patentable distinction over the prior art because such ranges are reasonably interpreted as characterizations of the effective amounts of the claimed compound for treating cancer as suggested and motivated by the prior art.

Renhowe *et al.* teach a genus of compounds that are small molecule inhibitors of vascular endothelial growth factor receptor tyrosine kinases for treating diseases characterized by angiogenesis, including cancer (col. 1, lines 11-21). Members of the VEGF subfamily of receptor tyrosine kinases are taught to induce vascular permeability and endothelial cell proliferation and to induce angiogenesis and vasculogenesis (col. 2, lines 13-16).

Accordingly, the inventors sought to develop compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, and/or inhibit vascular endothelial growth factor receptor tyrosine kinase (col. 3, lines 27-35). To this end, the inventors teach a genus of quinolinone compounds (col. 3, line 39 to col. 18, line 21), of which the instantly claimed compound is a specie and is explicitly recited as Example 109 at column 86, lines 64-66 and column 97, lines 23-24. This compound, along with a series of other compounds, is to have an IC_{50} value of less than 10 μM with respect to VEGFR1, VEGFR2, and bFGF (col. 101, lines 45-47).

With regard to claims 16-19 and 21-22, the compounds disclosed in Renhowe *et al.* may be formulated in pharmaceutical compositions comprising pharmaceutically acceptable carriers, excipients, binders, diluents, and the like (col. 57, lines 62-66) as well as thickeners, buffers, sweeteners, and flavoring agents (col. 59, line 1).

With regard to claim 23, the compounds of the invention may be formulated in compositions for various routes of administration (col. 57, line 62 to col. 60, lines 32), such as in injectable dosage forms (col. 59, lines 37-59).

With regard to claims 24-27, 31-35, and 50-51, specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). Any of the dosage forms containing effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 60, lines 38-40).

With regard to therapeutically effective doses, the inventors teach that these doses may vary depending on the route of administration and dosage form (col. 60, lines 41-42).

With regard to "treating", the inventors teach that this means, for example, within the context of treating patients in need of an inhibitor of VEGF-RTK, a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells (col. 60, lines 52-63).

With regard to claims 57 and 58, which recite metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one, the administration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one to a patient as suggested and motivated by Renhowe *et al.* will necessarily result in the "administration" of the metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as recited in the instant claims because such metabolites are formed, by definition, by the action of enzymes in the body of a patient administered 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one.

The inventors explicitly contemplate and teach a method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase comprising administering an effective amount of a pharmaceutical formulation according to the invention to a patient in need thereof (col. 61, lines 6-10 and claim 30) and a method for inhibiting tumor growth in a patient comprising administering an effective amount of a pharmaceutical

formulation according to the invention to a patient having a tumor (col. 61, lines 11-14). Such methods encompass the treatment therefore of any cancer or tumor in a patient, especially those cancers or tumors with cells expressing a receptor tyrosine kinase.

The FDA guidelines for the format and content of the human pharmacokinetic and bioavailability section of a New Drug Application teaches that biopharmaceutic studies are required by the Food, Drug, and Cosmetic Act (page 1). Such studies include pharmacokinetic studies assessing the time course of drug and major metabolite concentrations in blood and other body compartments (pages 3-4). The studies provided in support of a New Drug Application, the most critical information is that showing (by measurement of plasma drug levels) the rate of drug absorption and delivery to the systemic circulation, and the rate of elimination by metabolic or excretory processes (page 4). Pharmacokinetic parameters should include C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from each *in vivo* study (page 6).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a therapeutically effective amount of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one to a patient in need thereof (*e.g.*, a patient having a cancer or tumor with cells expressing VEGFR1, VEGFR2, and/or bFGF). In support of the obviousness of the claimed methods, the Examiner makes the following findings of fact:

(i) The instantly claimed compound and related compounds were known in the art and were known to inhibit at least VEGFR1, VEGFR2, and bFGF;

(ii) Inhibition of such receptor tyrosine kinases was suggested by the prior art to be useful in the treatment of cancers;

(iii) Therapeutically effective amounts of the claimed compound are suggested by the prior art to vary depending on the route of administration and dosage form; and

(iv) Determination of pharmacokinetic parameters such as C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from *in vivo* studies is a requirement before a new drug can be approved for use in human patients.

Thus, Renhowe *et al.* provide explicit teaching, suggestion, and motivation to administer the instantly claimed compound and structurally related compounds to patients in need thereof,

which patients include those having a cancer or tumor with expressing a vascular endothelial growth factor receptor tyrosine kinase.

With regard to the claimed C_{max}, ng/mL, and AUC ranges as recited in the instant claims, although Renhowe *et al.* did not characterize the compounds of their invention with regard to pharmacokinetics, it is noted that the compounds of Renhowe *et al.* appear to be early in their clinical development. As such, the fact that Renhowe *et al.* had not yet administered the compounds of their invention to patients to determine the pharmacokinetics (*e.g.*, C_{max}, ng/mL, and AUC) is not evidentiary of the nonobviousness of the present rejection because Renhowe *et al.* teach administration of therapeutically effective amounts of the disclosed compounds to patients. As such, in the absence of a showing to the contrary, administration of a therapeutically effective amount of the claimed compound to a patient as suggested and motivated by Renhowe *et al.* will necessarily result in the claimed C_{max}, ng/mL, and AUC ranges. Further, such pharmacokinetic measurements are required by the FDA and thus their determination for any drug is an obvious step in the development of pharmaceutical agents.

In this regard, the state-of-art approach to developing novel pharmaceutical agents is to (i) identify compounds that inhibit or bind to a receptor of interest in treating a particular disease (as Renhowe *et al.* have done); (ii) verify through *in vitro* assays that the identified compounds do in fact inhibit or bind to a receptor of interest (as Renhowe *et al.* have done); (iii) determine the activity of the compounds in *in vitro* and *in vivo* models of the disease of interest; and (iv) characterize the pharmacokinetics of lead compounds to determine a dosing regimen for use in Phase I and Phase II clinical trials. Renhowe *et al.*, as noted above, have carried out the first two steps in the development of the disclosed quinolinone compounds for treating cancer. Applicants appear to have taken the next two obvious steps in the development of a compound of Renhowe *et al.*, namely demonstrating that a compound taught by Renhowe *et al.* to be useful in treating cancer or tumors is in fact therapeutically active both *in vitro* and *in vivo* (as suggested by Renhowe *et al.*) and determining therapeutically effective dosing regimens by characterizing the pharmacokinetics of the claimed compound through routine experimentation (as suggested by the FDA).

Claims 7-8 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) in view of **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"** (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18). as applied to claims 1-6, 9-13, 16-38, 49-51, 53-58, and 67-71 above, and further in view of **Berge *et al.*** (J. Pharm. Sci., 1977, vol. 66, no. 1, pages 1-19).

Renhowe *et al.* and the FDA Guidelines teach as discussed supra and are applied herein in their entirety for the same teachings. Claims 14 and 15 differ from Renhowe *et al.* and the FDA Guidelines in the recitation of a lactate salt of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one.

However, Berge *et al.* teach that the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form (page 1, left column). In this regard, Berge *et al.* teach a list of FDA approved commercially marketed salts, including the instantly claimed lactate salt (Table 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as taught in Renhowe *et al.* as a lactate salt. It is noted that Renhowe *et al.* teach that pharmaceutically acceptable salts and tautomers of the disclosed compounds are encompassed by their invention (col. 57, lines 64-65). The skilled artisan would have been motivated to do so because Renhowe *et al.* teach that pharmaceutically acceptable salts of the compounds of their invention may be used in compositions for treating patients and Berge *et al.* teach that lactate salts of pharmaceutical agents are suitable salts approved by the FDA. As such, the skilled artisan would have been imbued with at least a reasonable expectation that a lactate salt of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one could be formed and would be useful in the methods taught, suggested, and motivated by Renhowe *et al.* (*i.e.*, treatment of patients).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 9-15, 16-38, 49-51, 53-58, and 67-71 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of U.S. Patent No. 6,605,617. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase comprising administering an effective amount of a formulation comprising a compound of any of claims 1, 8, 15, or 22 as recited in claim 30 of the '617 patent encompasses the treatment of the claimed cancers using any amount of the instantly claimed compound that is "effective". As such, Applicant's characterization of the Cmax and AUC values of the instantly claimed compound is not seen as a patentable distinction over the method claimed in the '617 patent. Further, the specification of the '617 patent, when used as a dictionary to define the claimed "effective amount" states that specific dosages may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). Any of the dosage forms containing

effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 60, lines 38-40).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614